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Predicting carriage with extended-spectrum beta-lactamase-producing bacteria at hospital admission: a cross-sectional study

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Abstract

The prevalence of patients colonized with extended-spectrum beta-lactamase (ESBL)-producing bacteria increases, especially in long-term-care facilities (LTCFs). Identification of ESBL carriers at hospital admission is relevant for infection control measures and antibiotic therapy for nosocomial infections. We aimed to develop a prediction rule for ESBL carriage at hospital admission for patients admitted from home and LTCFs, and to quantify incidences of nosocomial infections caused by ESBL-producing bacteria. The ESBL-carrier status was determined of patients admitted from LTCFs and from home settings in four hospitals in the Netherlands using perianal swabs obtained within 48 hours of admission. Risk factors for ESBL carriage were assessed. Infections caused by ESBL-producing bacteria were identified retrospectively.

Among 1351 patients, 111 (8.2%) were ESBL carriers at admission: 50/579 (8.6%) admitted from LTCFs and 61/772 (7.9%) from home settings (p 0.63). Previous ESBL carriage and previous hospital admission were risk factors for ESBL carriage in multivariable analysis. The area under the curve of the receiver operating characteristic curve of the model was 0.64 (95% CI 0.58–0.71). Presence of $\geq$1 risk factor (n = 803; 59%) had sensitivity of 72%. Incidences of nosocomial infections caused by ESBL-producing bacteria were 45.5/10 000 and 2.1/10 000 admission days for ESBL carriers and non-carriers, respectively (p <0.05). In conclusion, prevalence of ESBL carriage at hospital admission was 8.2%, and was comparable among patients admitted from LTCF and home. A clinically useful prediction rule for ESBL carriage at admission could not be developed. The absolute incidence of nosocomial infections by ESBL-producing bacteria was low, but higher among patients carrying ESBL-producing bacteria at the time of hospital admission.

Keywords: Carriage, Enterobacteriaceae, ESBL, hospital admission, risk factors
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Introduction

Infections due to extended-spectrum beta-lactamase (ESBL)-producing bacteria are increasing worldwide [1,2], and are often preceded by asymptomatic carriage, i.e. colonization [3]. Prevalence of ESBL carriage in hospitalized patients and patients treated in long-term-care facilities (LTCFs) have been reported to be as high as 27% [4,5], and the prevalence of ESBL-carriage in non-hospitalized subjects seems to be increasing (www.isis-web.nl) [6,7].

Identification of ESBL carriers at hospital admission is relevant for implementing appropriate infection control measures and selecting empirical antibiotic therapy in case of nosocomial infection (http://www.swab.nl/richtlijnen).

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Previous hospital stay, severity of illness, time in the intensive care unit (ICU), intubation and mechanical ventilation, urinary or arterial catheterisation, previous exposure to antibiotics, and urinary tract infections have been identified as risk factors for acquisition of ESBL-producing bacteria during hospital stay [8–11]. In addition, LTCF residents are considered to have an increased risk of ESBL carriage due to the presumed high risk for acquisition and transmission of ESBL-producing bacteria in these settings, facilitated by antibiotic use, understaffing, and failing infection control measures [12]. However, risk factors for ESBL carriage at the time of hospital admission have been determined only prospectively in unselected hospitalized patients in 2006 [12].

We, therefore, prospectively determined the prevalence of ESBL carriage in consecutively admitted patients coming from LTCFs and home settings, and aimed to develop a prediction rule for ESBL carriage at hospital admission. In addition, the incidence of infections with ESBL-producing bacteria was determined in patients identified as ESBL carriers at hospital admission and non-carriers.

Methods

Setting and patients

This study was conducted in four hospitals (one tertiary care teaching hospital and three general teaching hospitals) in the Netherlands between January 2010 and December 2012. All patients admitted from LTCFs (nursing homes and rehabilitation facilities) to one of the surgery or general medicine wards were eligible for inclusion, as were patients admitted from home during three periods of 9 weeks, at the beginning, middle, and end of the study period in each hospital. Exclusion criteria were age <18 years, an expected hospital stay <48 hours, admission from another hospital, and inability to fill out the questionnaire and not having any relatives present to do so. The institutional regulatory board approved the study and considered the culture scheme as part of "usual care."

Study design

This was a prospective study. Perianal swabs, obtained within 48 hours of admission, were inoculated on an ESBL Brilliance plate (Thermo Fisher Scientific, Loughborough, UK) to detect ESBL-producing strains and on MacConkey agar (Thermo Fisher Scientific) as a control for adequate sampling. In case of no growth on both plates, patients were excluded from analysis. Isolates obtained from the ESBL Brilliance plates were investigated by microarray analysis (Check-Points, Wageningen, the Netherlands) for the presence of ESBL genes. DNA isolation was performed using Ultraclean Microbial DNA Isolation Kit (Mo Bio Laboratories Inc., Carlsbad, CA, USA) according to the instructions of the manufacturer.

Species identification was performed using MALDI-TOF (Bruker Daltonik, Bremen, Germany). Susceptibility was determined by disk diffusion (ROSCO, Taastrup, Denmark) for all antibiotics except for fosfomycin, which was tested by Etest (BioMérieux, Marcy l'Etoile, France). Results were interpreted using European Committee on Antimicrobial Susceptibility Testing breakpoints.

A standardized questionnaire was used to collect information on use of antibiotics or immunosuppressants, surgical procedures, presence of indwelling devices, travel to foreign countries, and work-related contact with animals in the year before admission. Patients were encouraged to mark "unknown" if they were uncertain whether they used antibiotics or immunosuppressants. In case patients declared use or were uncertain about use, this information was retrieved from their pharmacy records. In addition, the pharmacy records of 50 patients who reported no use were randomly checked.

Departments were instructed to keep records of the number of patients that were not approached or refused participation.

Microbiology databases were used to identify ESBL carriage before admission, as well as presence of clinical cultures yielding ESBL-producing bacteria during hospital stay. Hospital-acquired infections (HAI) caused by ESBL-producing bacteria were defined as presence of a clinical culture with ESBL-producing bacteria obtained more than 48 hours after hospital admission that was treated by the clinician with antibiotics. Community-acquired infections (CAI) caused by ESBL-producing bacteria were defined as presence of a clinical culture with ESBL-producing bacteria obtained within 48 hours after hospital admission that was treated by the clinician with antibiotics.

Statistical analysis

Statistical analyses were performed by χ^2 test or Fisher's exact test for categorical data, and Student's *t* test or Mann-Whitney *U* test for continuous data. Backward multivariate logistic regression analysis was conducted on variables significantly associated with carriage of ESBL-producing bacteria in univariate analysis, after exclusion of multicollinearity, as well as some other suspected important predictors. Variables with a p-value <0.10 were included in the model. The model's predictive ability was examined using the area under the receiver operating characteristics curve. Calibration of the model was estimated by the Hosmer-Lemeshow statistic in which a p-value >0.20 indicates adequate fit.

Missing data were replaced by multiple imputation (automatic method) before univariate analysis. To obtain a weighted score for the prediction rule, the regression coefficients of the

TABLE 1. Possible risk factors in ESBL-positive and -negative patients, admitted from home and LTCFs, and missing values before multiple imputation

Characteristics		Patients admitted from home		Patients admitted from LTCFs	
		ESBL-negative *n* (%) *n* = 711	ESBL-positive *n* (%) *n* = 61	ESBL-negative *n* (%) *n* = 529	ESBL-positive *n* (%) *n* = 50
Sex	Female	388 (55)	28 (46)	338 (64)	23 (46)
	Male	323 (45)	33 (54)	191 (36)	27 (54)
	Missing	0 (0)	0 (0)	0 (0)	0 (0)
Age, mean years (SD)		64 (18)	67 (15)	82 (12)	81 (12)
Previous AB (1 year)	Yes	401 (56)	25 (41)	298 (56)	33 (66)
	No	307 (43)	36 (59)	229 (43)	17 (34)
	Missing	3 (0)	0 (0)	2 (0)	0 (0)
Previous IS (1 year)	Yes	113 (16)	14 (23)	110 (21)	7 (14)
	No	597 (84)	46 (75)	418 (79)	43 (86)
	Missing	1 (0)	1 (2)	1 (0)	0 (0)
Previous admissions (1 year)	Yes	268 (38)	33 (54)	208 (39)	26 (52)
	No	442 (62)	28 (46)	317 (60)	23 (46)
	Missing	1 (0)	0 (0)	4 (1)	1 (2)
Catheter	Yes	63 (9)	7 (11)	90 (17)	16 (32)
	No	647 (91)	54 (89)	435 (82)	34 (68)
	Missing	1 (0)	0 (0)	4 (1)	0 (0)
Previous surgery (1 year)	Yes	172 (24)	20 (33)	104 (20)	15 (30)
	No	538 (76)	41 (67)	421 (80)	35 (70)
	Missing	1 (0)	0 (0)	4 (1)	0 (0)
Previous travel (1 year)	Yes	234 (33)	16 (26)	30 (6)	2 (4)
	No	466 (66)	44 (72)	494 (93)	48 (96)
	Missing	11 (2)	1 (2)	5 (1)	0 (0)
Occupation with animal contact	Yes	13 (2)	1 (2)	1 (0)	1 (2)
	No	642 (90)	55 (90)	528 (100)	49 (98)
	Missing	56 (8)	5 (8)	0 (0)	0 (0)
Previous ESBL-carriage (1 year)	Yes	5 (1)	7 (11)	6 (1)	4 (8)
	No	706 (99)	54 (89)	523 (99)	46 (92)
	Missing	0 (0)	0 (0)	0 (0)	0 (0)

AB, use of antibiotics; ESBL, extended-spectrum beta-lactamase; IS, use of immunosuppressants; LTCF, long-term-care facilities.

predictive variables were rounded to the nearest number ending in .5 or .0, resulting in a weighted score.

Isolates that grew on the ESBL Brilliance plate, but that were not available for genotyping, were assumed ESBL positive. All analyses were performed using SPSS 20 (IBM, Armonk, NY, USA).

Results

In total, 1531 patients were screened for ESBL carriage. Of these, 180 patients were excluded from the study because their cultures on both the MacConkey and the ESBL Brilliance agar were negative. Therefore, a total of 1351 patients were included: 579 (42.9%) admitted from >100 different LTCFs and 772 (57.1%) from the community. Patient characteristics are depicted in Table 1. Populations admitted from home and LTCFs at the four sites did not differ significantly in gender or previous ESBL carriage. In one hospital, the mean age for patients from home was higher (60 vs. 62 vs. 64 vs. 76 years; p <0.01 for the last hospital, as compared to the other hospitals); as for another hospital, the mean age for patients from LTCFs was lower (74 vs. 81 vs. 82 vs. 86 years; p <0.01 for the first hospital, as compared to the other hospitals). In one hospital, patients from home had fewer previous hospital admissions (19% vs. 26% vs. 34% vs. 34%; p <0.01 for the first hospital as compared to the last two). Among populations admitted from an LTCF, no statistically significant differences were observed in previous hospital admissions. For 71% of patients from LTCFs and 55% of patients from home, information on use of antibiotics and immunosuppressants was retrieved from pharmacy records. Among the 50 patients checked that declared no use, only one had antibiotics in the year before admission and none in the 6 months before admission.

The prevalence of ESBL carriage at hospital admission was 7.9% (*n* = 60; range per hospital 5.4–10.3%; n.s.) and 8.6% (*n* = 51; range per hospital 5.3–18.8%; n.s.) for patients admitted from home and LTCFs, respectively. There was no significant difference in ESBL prevalence among the four sites. The prevalence of 18.8% (6/32) in one hospital among patients from LTCFs resulted mostly from patients admitted from a single LTCF with a known high endemic prevalence of ESBL carriage. Four of the six patients in this hospital, being ESBL-positive at admission, originated from this LTCF.

Species identification and susceptibility testing was available for 109 isolates from 97 patients. Susceptibility rates were for tobramycin 77%, gentamicin 85%, ciprofloxacin 62%, trimethoprim/sulfamethoxazole 35%, amikacin 100%, fosfomycin 84%, and nitrofurantoin 77%.

Distribution of species and ESBL genes is shown in Table 2. No differences were observed in distribution of genes between patients admitted from home and LTCFs.

TABLE 2. Distribution of species and ESBL genes[a]

Species	Total $n = 109$ n (%)	CTX-M-1 group n (%)	CTX-M-9 group n (%)	SHV-4 group n (%)	TEM-3 group n (%)	SHV-2 group n (%)	CTX-M-2 group n (%)	SHV-4 group & CTX-M-9 group n (%)
Escherichia coli	74 (68)	48 (65)	11 (15)	8 (11)	6 (8)	1 (1)		
Klebsiella pneumoniae	14 (13)	10 (71)	2 (14)			2 (14)		
Enterobacter cloacae	13 (12)	3 (23)	7 (54)		1 (8)			2 (15)
Citrobacter freundii	3 (3)	2 (67)	1 (33)					
Pseudomonas putida	2 (2)	2 (100)						
Enterobacter asburiae	1 (1)	1 (100)						
Kluyvera ascorbata	1 (1)						1 (100)	
Morganella morganii	1 (1)		1 (100)					
Total	109 (100)	66 (61)	22 (20)	8 (7)	7 (6)	3 (3)	1 (1)	2 (2)

ESBL, extended-spectrum beta-lactamase.
[a]In two isolates, both CTX-M-9 and SHV-4 genes were detected.

In univariate analysis, eight potential risk factors for ESBL carriage were identified. These, together with age and patient origin (LTCF or community), were included in multivariate analysis after exclusion of multicollinearity, which yielded documented ESBL carriage within 1 year before admission, hospital admission in the previous 6 months, and male gender as associated with ESBL carriage (Table 3). Twenty-two (2%) of 1351 patients had been identified as ESBL carriers in the 12 months before hospital admission, and 11 (50%) were still ESBL carriers at hospital admission, yielding a sensitivity of 10% and positive predictive value of 50% for prior ESBL carriage. The area under the receiver operating characteristics curve of the model based on these predictors was 0.64 (95% CI 0.58–0.71). The goodness of fit was adequate (Hosmer-Lemeshow statistic p 0.60).

A strategy of screening patients with at least two statistically significant risk factors (15% of all patients) would identify 31% of ESBL carriers, and screening all patients with at least one risk factor (59% of all patients) would identify 72% of ESBL carriers (Table 4). Thirty-one of the 111 patients carrying ESBL-producing bacteria (28%) had none of the risk factors identified in multivariate analysis.

Of these 31, 18 (58%) came from home and 13 from a LTCF. The median age was 82 years (interquartile range 66–89 years). Nine had travelled to foreign countries, but only four outside Europe (one to Korea and New Zealand, one to Aruba and Cuba, and two to Turkey). One worked with animals.

Of the 1351 patients included, 20 (1.5%) developed an infection with ESBL-producing bacteria: 15 a CAI and five an HAI. From the 111 patients identified as intestinal carriers at admission, 13 (12%) developed a CAI and three an HAI (2%) with ESBL-producing bacteria. From the 1240 patients not identified as intestinal carriers, two developed a CAI (0.2%) and two an HAI (0.2%) with ESBL-producing bacteria. The incidence densities of hospital-acquired infection with ESBL-producing bacteria were 45.5 (95% CI 9.4–132.8) and 2.1 (95% CI 0.26–7.7) per 10 000 admission days for patients carrying and not carrying ESBL-producing bacteria at hospital admission.

TABLE 3. Predictors of ESBL carriage at admission

Variable	Univariate analysis OR (95% CI)	Multivariate analysis final model OR (95% CI)
Patient admitted from LTCF	1.11 (0.75–1.66)[a]	
Male	1.58 (1.06–2.36)[b]	1.49 (0.99–2.23)
Age (years)	0.99 (0.98–1.01)[a]	
ESBL <1 year	12.99 (5.49–30.47)[b]	11.35 (7.22–17.84)
Penicillins <6 months	2.61 (1.54–4.44)[b]	
Cephalosporins <6 months	1.78 (1.17–2.70)[b]	
Fluoroquinolones <6 months	2.03 (1.26–3.28)[b]	
Macrolides <6 months	1.54 (0.79–3.00)	
Carbapenems <6 months	2.79 (0.69–11.25)	
Tetracycline <6 months	1.82 (0.91–3.64)	
Aminoglycosides <6 months	2.02 (0.40–10.27)	
Sulfonamides/trimethoprim <6 months	1.04 (0.49–2.22)	
Immunosuppressants <6 months	1.27 (0.76–2.11)	
Admissions <6 months	2.32 (1.55–3.47)[b]	2.13 (1.41–3.21)
External device	1.84 (1.12–3.03)[b]	
Surgery	1.57 (1.02–2.41)[b]	
Travel <1 year	0.69 (0.40–1.18)	
Occupation with animal contact	1.41 (0.34–5.83)	

ESBL, extended-spectrum beta-lactamase; LTCF, long-term-care facilities.
[a]Variables included in multivariable analysis based on evidence.
[b]Variables included in multivariable analysis based on OR.

TABLE 4. Test characteristics of screening based on risk factors

Risk factors	Sensitivity	Specificity	PPV	NPV	% Needed to screen
Individual risk factors					
Male gender	0.51	0.59	0.10	0.93	42
Previous admission	0.49	0.70	0.13	0.94	31
Previous ESBL carriage	0.10	0.99	0.50	0.92	2
Number of risk factors					
≥1	0.72	0.42	0.10	0.94	59
≥2	0.31	0.87	0.17	0.93	15
≥3	0.054	1.00	0.75	0.92	1
Weighted score[a]					
≥1	0.72	0.42	0.10	0.94	59
≥2	0.51	0.70	0.13	0.94	32
≥3	0.33	0.86	0.17	0.94	16
≥6	0.10	0.99	0.50	0.92	2
≥7	0.09	1.00	0.67	0.92	1
≥8	0.07	1.00	0.67	0.92	1
≥9	0.05	1.00	0.75	0.92	1

ESBL, extended-spectrum beta-lactamase; NPV, negative predictive value; PPV, positive predictive value.
[a]Weighted score: male gender 1 point, previous admission 2 points, previous ESBL carriage 6 points.

One patient without positive screening cultures at admission acquired ESBL-positive cultures during hospitalization but was not treated.

Discussion

In this prospective, multicentre study of 1351 patients, the prevalence of ESBL carriage at hospital admission was 8.2%, and was comparable among patients admitted from LTCFs and home settings. Despite the study size and detailed data collection, it was not possible to develop a clinically useful prediction rule for ESBL carriage at hospital admission. These findings underscore the widespread occurrence of ESBL carriage and the difficulties for developing targeted screening strategies to identify ESBL carriers. Incidence of nosocomial infections by ESBL-producing bacteria was higher in ESBL carriers than in non-carriers.

The observed prevalence of ESBL carriage of 8.2% is remarkably consistent with reported prevalences of 8.6% and 9.0% among healthy subjects in the Netherlands, with a mean age of 33 and 43 years, respectively, screened before travel departure to high-risk areas between 2010 and 2012. Furthermore, the distribution of ESBL genes was comparable to the reported distribution in clinical isolates from Dutch patients in 2009 [13], suggesting that the molecular epidemiology of ESBL-producing Enterobacteriaceae has remained unchanged from 2009 to 2012.

In this study, prior ESBL carriage, hospital admission within the last 6 months, and male gender were associated with ESBL carriage, which confirms results from previous studies [9,14,15]. Although male gender has been identified as a risk factor for ESBL carriage in previous studies as well, the biologic substrate remains unknown [12]. We could not confirm findings from two studies in Israel in which nursing home residence was a risk factor for ESBL carriage at the time of hospital admission [9,14]. Possibly, this is a result of the restrictive antibiotic policy in the Netherlands. Although antibiotic use in LTCFs is higher than in the community, this is still very low compared to other countries [16,17]. Neither could we confirm use of antibiotics, diabetes mellitus, connective tissue disease, and liver failure as risk factors [11]. Furthermore, numbers of patients with an occupation involving animal contacts or that had travelled to so-called high-risk countries were too low in the current study to be identified as risk factor.

We could not develop a clinically useful prediction rule to identify patients with ESBL carriage at the time of hospital admission. The obtained area under the curve of the identified risk factors for ESBL carriage at admission was 0.65 (95% CI 0.63–0.66). Increasing the positive predictive value toward clinically useful values would reduce the sensitivity to unacceptable low levels. Previous attempts in retrospective studies in single centres or single wards, and with fewer patients enrolled, also failed to develop such a prediction rule [10,14,18]. This is possibly the result of heterogeneous transmission routes that include nosocomial, household, and food contacts. Antibiotic use and host susceptibility add further complexity.

In the absence of a useful prediction rule, screening all patients at admission could be considered. However, there is currently no rapid detection tool available for ESBL carriage, implying that in case of universal screening, patients should either be pre-emptively isolated while awaiting culture results or treated without precautions until results are available, which is suboptimal for infection control. However, in an international study in ICUs, universal screening and isolation of detected carriers was not associated with a statistically significant reduction in ICU-acquired carriage with highly resistant Enterobacteriaceae, as compared to isolation of detected carriers alone [19]. Neither do the results of this study support universal screening. Although the risk of HAIs with an ESBL-producing pathogen was significantly higher in patients with documented carriage of ESBL-producing bacteria at the time of hospital admission, the absolute risk of infection was low. In addition, three of the five patients with an HAI were not colonized with ESBL-producing bacteria at the time of hospital admission, and none of the observed infections could be considered invasive. Furthermore, pre-emptive isolation is probably not feasible in most settings. The association between ESBL carriage at admission and a higher risk to develop an HAI with ESBL-producing bacteria, as compared to non-carriers, was also observed in patients receiving liver transplants in France [20]. Infections caused by ESBL-producing bacteria occurred in 45% and 4% of patients identified as ESBL carriers and non-carriers, respectively, before transplantation. In contrast, such an association was not found in neutropenic patients with hematologic malignancies, as the total number of patients with documented infection was only three [21].

Strengths of our study include the sample size of 1351 patients, the multicentre design, the inclusion of patients admitted to different hospital wards, the enrichment of patients from LTCFs, and the protocolized data collection.

Study limitations include the potential for inclusion bias, as patients with inability to fill out questionnaires were excluded and severely ill patients were probably more likely to refuse participation. Although departments were instructed to record how many patients were not approached or refused participation, these data appeared to be unreliable. Possibly, inclusion of comorbidities could have improved the prediction rule. Although the ESBL microarray has been shown to match well

to the prevalent ESBL genes in the Netherlands, some ESBL-producing strains might have been missed, as not all ESBL types can be identified by the ESBL microarray [22]. Furthermore, the determination of HAIs caused by ESBL-producing bacteria was a post hoc analysis, based on retrospective chart review.

In conclusion, prevalence of ESBL carriage at admission was 8.2%, without elevated risk for patients from LTCFs. A clinically useful prediction rule for ESBL carriage at admission could not be developed. The incidence of nosocomial infections by ESBL-producing bacteria was higher in ESBL carriers than in non-carriers, but the absolute risk of an infection among ESBL carriers was low.

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